I. AMENDMENTS

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Currently Amended) A method of ~~inhibiting proteolytic conversion of inactive TGF-β to active TGF-β by a cation independent mannose 6 phosphate (CIM6P) receptor expressed on a cytotrophoblast cell~~ improving a physiological characteristic in a pregnant female mammal, the physiological characteristic being selected from the group consisting of placental growth, placental function, placental development and placental differentiation, the method comprising administering ~~a differentiation factor selected from the group consisting of IGF-II, a precursor of IGF-II, an isomer of IGF-II and an analog of IGF-II in an amount sufficient to promote binding of said differentiation factor to said CIM6P receptor and thereby inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said receptor~~ an effective amount of IGF-II to said pregnant female mammal in the first half of pregnancy, ~~and thereby improve~~ whereby said characteristic in said pregnant female mammal is improved.

Claim 2. (Currently amended) The method of Claim 1, wherein said ~~administration of said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non migratory or non invasive cell type~~ effective amount of IGF-II comprises an amount sufficient to promote binding of said IGF-II to a cation independent mannose 6 phosphate receptor expressed on a cytotrophoblast cell.

Claim 3. (Currently Amended) The method of Claim 1, wherein said ~~differentiation factor is administered to an embryo produced by in vitro fertilization for implantation into a female mammal~~ IGF-II is administered to said pregnant female mammal by subcutaneous delivery.

Claim 4. (Currently Amended) The method of Claim 1, wherein said ~~differentiation factor is administered to a pregnant female mammal so as to inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said cytotrophoblast cells in said female mammal~~ IGF-II is administered to said pregnant female mammal by vaginal pessary.

Claim 5. (Currently Amended) The method of Claim 4, wherein said ~~differentiation factor is administered to said pregnant female mammal in the first half of pregnancy~~ IGF-II is administered to said pregnant female mammal by subcutaneous delivery and vaginal pessary.

Claim 6. (Cancelled)

Claim 7. (Currently amended) The method of Claim [[4]] 1, wherein said pregnant female mammal is selected from the group consisting of a human, a horse, a cow, a pig, a goat and a sheep.

Claim 8. (Withdrawn) A method of preventing the implantation of an embryo in the uterine decidual endometrium, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β by administration of a differentiation factor selected from the group consisting of latent TGF-β, a TGF-β analogue and an antibody specific against IGF-II that inhibit the interaction between IGF-II and CIM6P.

Claim 9. (Withdrawn) A method of regulating differentiation and migration of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β by administration of an differentiation factor selected from the group consisting of IGF-II, an IGF-II analogue and an antibody specific against latent TGF-β that promote the interaction between IGF-II and CIM6P.

Claim 10. (Withdrawn) A method of promoting terminal differentiation of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and exposing said cells to reduced levels of IGF-II, whereby the stem cell CIM6P receptors are able to bind latent TGF-β and thereby promote the activation of TGF-β.

Claim 11. (Withdrawn) A method of promoting stem cell division and stem cell migration, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and exposing said cells to increased levels of IGF-II, whereby the stem cell CIM6P receptors are unable to bind latent TGF-β and thereby inhibiting the activation of TGF-β.

Claim 12. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells or stem cells to differentiate and migrate, the method comprising determining in a mother, father or an embryo the presence of a polymorphic form of a gene wherein the level of expression of said gene serves to regulate the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and, whereby the CIM6P receptors have altered ability to bind latent TGF-β and thereby altered ability to activate TGF-β.

Claim 13. (Withdrawn) The method of claim 12, wherein said gene is selected from the group consisting of an insulin-like growth factor II gene, a urokinase plasminogen activator gene, a urokinase plasminogen activator receptor gene, a CIM6P (type-2 IGF) receptor gene, a TGF-β gene, a plasminogen gene and any polymorphic forms thereof.

Claim 14. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells to differentiate and migrate, the method comprising determining in a mother, father or embryo the sequence of nucleotides in the DNA near the insulin-like growth factor II gene to thereby determine the capacity of the cytotrophoblast to migrate into the uterine decidua and the capacity

of the placenta to transport substrates to the embryo, said insulin-like growth factor II gene comprising the insulin (INS) variable number of tandem repeats (VNTR).

Claim 15. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of messenger RNA transcribed from the insulin-like growth factor II gene in an embryo.

Claim 16. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein secreted by a mammalian embryo.

Claim 17. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein circulating in maternal and paternal blood.

Claims 18-29. (Cancelled)

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Claim 2. (Currently amended) The method of Claim 1, wherein said ~~administration of said differentiation factor inhibits said cytotrophoblast cell from differentiating from a migratory or invasive cell type to a non-migratory or non-invasive cell type~~ effective amount of IGF-II comprises an amount sufficient to promote binding of said IGF-II to a cation independent mannose 6 phosphate receptor expressed on a cytotrophoblast cell.

Claim 3. (Currently Amended) The method of Claim 1, wherein said ~~differentiation factor is administered to an embryo produced by in vitro fertilization for implantation into a female mammal~~ IGF-II is administered to said pregnant female mammal by subcutaneous delivery.

Claim 4. (Currently Amended) The method of Claim 1, wherein said ~~differentiation factor is administered to a pregnant female mammal so as to inhibit proteolytic conversion of inactive TGF-β to active TGF-β by said cytotrophoblast cells in said female mammal~~ IGF-II is administered to said pregnant female mammal by vaginal pessary.

Claim 5. (Currently Amended) The method of Claim 4, wherein said ~~differentiation factor is administered to said pregnant female mammal in the first half of pregnancy~~ IGF-II is administered to said pregnant female mammal by subcutaneous delivery and vaginal pessary.

Claim 6. (Cancelled)

Claim 7. (Currently amended) The method of Claim [[4]] 1, wherein said pregnant female mammal is selected from the group consisting of a human, a horse, a cow, a pig, a goat and a sheep.

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Claim 9. (Withdrawn) A method of regulating differentiation and migration of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β by administration of an differentiation factor selected from the group consisting of IGF-II, an IGF-II analogue and an antibody specific against latent TGF-β that promote the interaction between IGF-II and CIM6P.

Claim 10. (Withdrawn) A method of promoting terminal differentiation of embryonic stem cells or adult stem cells, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and exposing said cells to reduced levels of IGF-II, whereby the stem cell CIM6P receptors are able to bind latent TGF-β and thereby promote the activation of TGF-β.

Claim 11. (Withdrawn) A method of promoting stem cell division and stem cell migration, the method comprising regulating the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and exposing said cells to increased levels of IGF-II, whereby the stem cell CIM6P receptors are unable to bind latent TGF-β and thereby inhibiting the activation of TGF-β.

Claim 12. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells or stem cells to differentiate and migrate, the method comprising determining in a mother, father or an embryo the presence of a polymorphic form of a gene wherein the level of expression of said gene serves to regulate the competition for binding to the cation independent mannose-6-phosphate (CIM6P) receptor between IGF-II and latent TGF-β and, whereby the CIM6P receptors have altered ability to bind latent TGF-β and thereby altered ability to activate TGF-β.

Claim 13. (Withdrawn) The method of claim 12, wherein said gene is selected from the group consisting of an insulin-like growth factor II gene, a urokinase plasminogen activator gene, a urokinase plasminogen activator receptor gene, a CIM6P (type-2 IGF) receptor gene, a TGF-β gene, a plasminogen gene and any polymorphic forms thereof.

Claim 14. (Withdrawn) A method of diagnosing a predisposition of cytotrophoblast cells to differentiate and migrate, the method comprising determining in a mother, father or embryo the sequence of nucleotides in the DNA near the insulin-like growth factor II gene to thereby determine the capacity of the cytotrophoblast to migrate into the uterine decidua and the capacity

of the placenta to transport substrates to the embryo, said insulin-like growth factor II gene comprising the insulin (INS) variable number of tandem repeats (VNTR).

Claim 15. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of messenger RNA transcribed from the insulin-like growth factor II gene in an embryo.

Claim 16. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein secreted by a mammalian embryo.

Claim 17. (Withdrawn) A method of determining the ability of cytotrophoblast cells to differentiate and migrate, the method comprising measuring the amount of insulin-like growth factor II protein circulating in maternal and paternal blood.

Claims 18-29. (Cancelled)